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<b>(21) International Application Number:</b> PCT/JP99/04046 <b>(22) International Filing Date:</b> 26 July 1999 (26.07.99) <b>(30) Priority Data:</b> 10/217517      31 July 1998 (31.07.98)      JP <b>(71) Applicant (for all designated States except US):</b> OTSUKA PHARMACEUTICAL CO., LTD. [JP/JP]; 9, Kandatsukasa-cho 2-chome, Chiyoda-ku, Tokyo 101-8535 (JP). <b>(72) Inventors; and</b> <b>(73) Inventors/Applicants (for US only):</b> ONISHI, Yoshinao [JP/JP]; 4-56, Shimosuketo-cho, Tokushima-shi, Tokushima 770-0805 (JP). DOI, Hirofumi [JP/JP]; 2-16, Suehiro 1-chome, Tokushima-shi, Tokushima 770-0866 (JP). ODOMI, Masaaki [JP/JP]; #603, 19-1 Nakazu-cho 3-chome, Tokushima-shi, Tokushima 770-0856 (JP). <b>(74) Agent:</b> KAMEI, Hirokatsu; AI Association of Patent and Trademark Attorneys, Jyutakukinyukoko-Sumitoseimei Building, 12F, 5-20, Minamihommachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0054 (JP).		<b>(81) Designated States:</b> AU, BR, CA, CN, ID, KR, MX, SG, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITION HAVING IMPROVED TASTE <b>(57) Abstract</b> <p>Disclosed is a pharmaceutical composition comprising a drug-containing substance wherein an unpleasant taste of the drug is masked out, and a gelling agent, wherein said pharmaceutical composition is converted into a jelly-like preparation containing the above drug-containing substance dispersed therein by dissolving in water. Said pharmaceutical composition is reduced in an unpleasant taste of a drug having an unpleasant taste such as bitter taste, puckery taste, acid taste, etc. and its ease of taking is improved.</p>		

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## DESCRIPTION

## PHARMACEUTICAL COMPOSITION HAVING IMPROVED TASTE

## Technical Field

5           The present invention relates to a pharmaceutical composition for internal use, wherein an unpleasant taste of a drug having an unpleasant taste such as bitter taste, puckery taste, acid taste, etc. is reduced and its ease of taking is improved. The pharmaceutical  
10 composition has such a characteristic that the unpleasant taste is significantly inhibited and reduced on taking it and control of the dose is simple and, therefore, it is a pharmaceutical composition suited particularly for a child drug dosage form.

## 15 Prior Art

          Among dosage forms of drugs, a dry syrup prepared by adding water on taking is effective for manufacturing a preparation by using drugs which are unstable in water. Furthermore, the dry syrup is often used as a child  
20 dosage form because of its flexibility of the dose and good ease of taking.

          The dry syrup includes, for example, those converted into a solution and those converted into a suspension, when adding water. When manufacturing the  
25 preparation, the form is selected according to physical

properties such as solubility of the drug, and purpose in the preparation effect such as sustained release. In the case where the drug has an unpleasant taste such as bitter taste, there can be employed the form of a  
5 suspending syrup obtained by forming the drug into solid particles wherein the taste of the drug is masked out by any method, and dispersing the solid particles.

As the method of reducing the bitter taste of the drug in the suspending dry syrup, there have hitherto  
10 been developed a method of changing a salt of original drug (Japanese Unexamined Patent Publication Nos. 295422/1992, 327526/1992 and 139996/1993), a method of using a derivative (WO92/06991) and a method of inhibiting dissolution by containing a drug in an  
15 insoluble base (Japanese Unexamined Patent Publication Nos. 95719/1979, 303928/1988, 187629/1992, 288821/1990, 327528/1992 and 501027/1994). In all techniques, there was a problem that, when inhibition degree of dissolution is too large, release in the gastrointestinal tract is  
20 not quickly conducted and the bioavailability of the drug is lowered.

It is an important object to reconcile conflicting conditions such as masking of the bitter taste and good release in the gastrointestinal tract in good balance in  
25 the development of the dosage form of drugs. Recently,

there has been suggested a technique capable of masking the taste for several hours to several days after suspending the drug in water without deteriorating the bioavailability of the drug (Japanese Unexamined Patent  
5 Publication No. 76517/1995).

However, according to these prior arts developed on the assumption that the bioavailability of the drug is obtained persistently, it is impossible to completely inhibit the dissolution of the drug, which occurs until  
10 the drug is taken after suspending particles containing the drug. Therefore, these prior arts are effective for a drug having low water solubility and a drug having high threshold value of bitter taste because patients do not feel the bitter taste even if a small amount of the drug  
15 is dissolved. However, in the case of a drug having high water solubility and low threshold value of bitter taste, the bitter taste is caused by this dissolution of a trace amount of the drug. The suspending syrup has a drawback that particles are remained in the mouth, thereby causing  
20 an unexpected bitter taste, sometimes.

Thus, in the case of the drug which is freely soluble in water and has strong bitter taste, it is difficult to prepare an oral solid medicine having both two conditions such as masking of the taste and good  
25 release in the gastrointestinal tract, or a dry syrup

based on the dry medicine, by using the prior art at present.

#### Disclosure of the Invention

In light of such problems of the prior art, the  
5 present invention has been developed.

Thus an object of the present invention is to provide a pharmaceutical composition, which can be easily taken without feeling an unpleasant taste of a drug by adding water to the drug having the unpleasant feel such  
10 as bitter taste before use, and which is superior in dissolution in the gastrointestinal tract.

The present inventors have intensively studied constantly to attain the above object, and found that, by taking drug-containing particles wherein the taste of the  
15 drug is masked out in a state of being dispersed and included in a jelly, it is possible to take even a drug, which is freely soluble in water and has a comparatively strong bitter taste, in a state where the bitter taste is sufficiently masked out without feeling the bitter taste.  
20 On the basis of such a knowledge, the present inventors have further studied and confirmed that a pharmaceutical composition suiting the above object can be prepared by combining a drug, wherein its unpleasant taste is masked out to such a degree that intrinsic bioavailability of  
25 the drug is not adversely affected, with a gelling agent

capable of being converted rapidly into a form of agar (jelly) when adding water.

That is, the present invention is a pharmaceutical composition comprising a drug-containing substance  
5 wherein an unpleasant taste of the drug is masked out, and a gelling agent. The pharmaceutical composition is converted into a jelly-like preparation containing the above drug-containing substance when being added to water.

10 Accordingly, the pharmaceutical composition of the present invention can be taken as a jelly-like preparation by adding water before use. That is, the present invention makes it possible to conduct masking of a drug having particularly strong bitter taste, which  
15 could not be sufficiently attained by the form of a suspending syrup according to the prior art, by taking, as a form on taking, the form of jelly wherein the drug whose unpleasant taste is masked out are dispersed and included. That is, according to the pharmaceutical  
20 preparation of the present invention, even if masking of the drug-containing substance is insufficient for securing the bioavailability thereby to cause leakage of the drug in the mouth on taking, diffusion of the drug is inhibited because a medium is in the form of jelly and,  
25 furthermore, the drug-containing substance is taken in a

state of being surrounded by a jelly and is hardly remained in the mouth. Therefore, appearance of the bitter taste derived from the drug is prevented. Since the jelly component is quickly diluted after transferring  
5 to the gastrointestinal tract, an influence is not exerted on the dissolution of the drug from the drug-containing substance and the release characteristics as a drug-containing substance unit are maintained, thereby to ensure the bioavailability of the drug.

10 Furthermore, since the pharmaceutical composition of the present invention is a preparation prepared before use, which is used in combination with water in a proper amount before use, unlike a coated drug such as conventional sugar-coated tablet, film-coated tablet,  
15 etc., it is possible to control the dose and is optimum for application to a child drug. Furthermore, the form of a jelly is easily taken and is also useful as an oral dosage form to infants, patients suffering from dysphagia, and aged persons.

#### 20 Brief Description of Drawings

Fig. 1 shows the solution out curve of the jelly composition of Example 11.

Fig. 2 shows the solution out curve of the jelly composition of Example 14.

#### 25 Mode for Carrying out the Invention



The pharmaceutical composition of the present invention will be described hereinafter. In the present specification, the particle diameter or particle size distribution of the drug show a value measured by the  
5 sieving method employed in Japanese Pharmacopoeia unless otherwise stated.

The drug to be used in the pharmaceutical composition according to the present invention is not specifically limited, but examples thereof include  
10 preferably drug which affords an unpleasant taste such as bitter taste, puckery taste, acid taste, etc., to the subject, and more preferably water-freely soluble drug which is easily dissolved in the mouth.

According to the present invention, the unpleasant  
15 taste of the drug is masked out to some extent by the prior art and the remaining unpleasant taste of the drug, which can not be completely masked out, is covered by taking the form of a jelly. Therefore, the present invention is particularly useful for a drug which is not  
20 sufficiently masked out by the prior art because of strong unpleasant taste and/or high water solubility.

More specifically, the drug includes, for example, antimicrobial drug which is generally considered to be bitter (e.g. pyridonecarboxylic acid synthetic  
25 antimicrobial drug, etc.); antibiotic which is generally

considered to be bitter [for example, penicillin antibiotic (e.g. bacampicillin, etc.), cephem antibiotic (e.g. cepaclor, cefotiam hexetil hydrochloride, ceftaram pivoxil, etc.), macrolide antibiotic (e.g. erythromycin, clarithromycin, josamycin, etc.) and other antibiotic (e.g. tetracycline, chloramphenicol, etc.) (including embodiments of salts thereof); antitussive/expectorant (e.g. tipepidine hibenzone, guaifenesin, diphenhydramine hydrochloride, promethazine hydrochloride, chlorpheniramine maleate, methylephedrine hydrochloride, dihydrocodeine phosphate, caffeine, anhydrous caffeine, etc.); tegafur, alacepril, sodium valproate, meclizine hydrochloride, aminophylline, calcium hopatenate, calcium pantothenate, phenobarbital, cimetidine, etilefrine hydrochloride, pirenzepine hydrochloride, diltiazem hydrochloride, piromidic acid hydrate, propranolol hydrochloride, flufenamic acid, chlorpromazine, digitoxin, promethazine hydrochloride, metoclopramide hydrochloride, acetaminophen, aspirin, ibuprofen, benzydramine hydrochloride, alprenolol hydrochloride, bifemelane hydrochloride, lidocaine, tolmetin sodium, nortriptyline hydrochloride, loperamide hydrochloride, etc.

The pyridonecarboxylic acid synthetic antimicrobial drug is particularly preferred. The pyridonecarboxylic

acid antimicrobial drug is generally referred to as newquinolone and examples thereof include synthetic antimicrobial drugs such as enoxacin, norfloxacin, ofloxacin, levofloxacin, cyprofloxacin, lomefloxacin, 5 tosusfloxacin, nadifloxacin, grepafloxacin, trovafloxacin and acid addition salts thereof. The acid addition salt include, for example, inorganic salt such as hydrochloride, nitrate, etc. and organic acid salt such as salts of citric acid, salicylic acid, tosylic acid, 10 mesylic acid, etc. These drugs may also be an anhydrate or a hydrate.

Generally, the above drugs are freely soluble in water and have strong bitter taste. Among them, grepafloxacin had such a problem that masking is not 15 easily conducted by a conventional method and is insufficient because of low threshold value of bitter taste, such as 1  $\mu\text{g/ml}$ , and high water solubility. Therefore, the drug used in the present invention is preferably a drug which is insufficiently masked out by 20 the conventional method because the threshold value of bitter taste is low (ranging from several to several tens  $\mu\text{g/ml}$ ) and the drug is freely soluble in water. The drug is preferably grepafloxacin described above, more preferably grepafloxacin hydrochloride, and particularly 25 preferably grepafloxacin hydrate.

The term "threshold value of bitter taste" used herein means a minimum concentration (w/v) of the drug wherein human generally feels bitter. For example, it can be determined from a minimum drug concentration of a  
5 test solution wherein at least one of subjects felt bitter after the subjects contain each of aqueous solutions (10 ml) of various drug concentrations in the mouth for 10 seconds.

It is possible to mask out the unpleasant taste of  
10 these drugs by using the masking method used usually in the medical field, thereby making it possible to prepare a drug-containing substance (see "Taste Masking in Oral Pharmaceuticals", Glenn M. Roy; Pharmaceutical Technology, APRIL, 1994, PP. 84-99).

15 More specifically, the masking method include the following method:

- (1) a method of granulating so as to disperse a drug in a matrix such as hydrogel or waxes;
- (2) a method of adsorbing a drug to a porous polymer or  
20 an ion exchange resin;
- (3) a method of masking by further granulating those obtained by the methods (1) and (2);
- (4) a method of film coating, for example,
  - (i) film-coating those obtained by granulating a drug,  
25 together with an excipient such as lactose, sucrose,

mannitol, cornstarch, etc. and a disintegrator such as croscarmellose sodium, etc., using a binder such as hydroxypropyl cellulose,

- (ii) film-coating those obtained by the methods (1) and  
5 (2), and  
(iii) film-coating those obtained by the method (3); and  
(5) a method of encapsulating by using a method of drying in liquid, a coacervation method, etc.

The hydrogel matrix base used herein includes, for  
10 example, gelatinized starch, partially gelatinized starch, gelatin, powdered acacia, methylcellulose, carmellose (carboxymethylcellulose), carmellose sodium (carboxymethylcellulose sodium), hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl pyrrolidone, low  
15 substituted hydroxypropylcellulose, sodium alginate, pullulan, dextrin, starch, pectin, carmellose calcium (carboxymethylcellulose calcium) or the like. The wax matrix base includes, for example, hydrogenated castor oil, hydrogenated soybean oil, glycerin fatty esters,  
20 sorbitan fatty esters or the like.

The porous polymer includes, for example, nonionic synthetic absorbent such as polystyrene, porous silica or the like. The ion exchange resin includes, for example, cation exchanger such as styrenesulfonic acid strong  
25 acidic cation exchange resin, acrylic weak-acidic cation

exchange resin, methacrylic cation exchange resin,  
methacrylic acid copolymer (e.g. Eudragit L, etc.),  
carboxyvinyl polymer, zeolites, synthetic zeolite,  
Permtite, etc.; anion exchanger such as styrenic strong-  
5 basic ion exchange resin, acrylic acid weak-basic ion  
exchange resin, hydrated iron oxide gel, etc.

The film-coating base and encapsulating base  
include, for example, polymers such as water-soluble  
polymer, water-insoluble polymer, acid-soluble polymer,  
10 enteric polymer, etc.

The water-soluble polymer includes, for example,  
powdered acacia, gelatin, sodium alginate,  
methylcellulose, carmellose, carmellose sodium,  
hydroxypropylcellulose, hydroxyethylcellulose,  
15 hydroxypropylmethylcellulose, polyvinyl pyrrolidone, etc.

The water-insoluble polymer includes, for example,  
ethylcellulose, purified shellac, waxes, etc.

The acid-soluble polymer includes, for example,  
aminoalkyl Methacrylate Copolymer E, polyvinyl acetal  
20 diethylaminoacetate, etc.

The enteric polymer includes, for example,  
carboxymethylethylcellulose, hydroxypropylmethylcellulose  
phthalate, hydroxypropylmethylcellulose acetate  
succinate, methacrylic acid copolymer, cellulose acetate  
25 phthalate, etc.

The drug-containing substance wherein the unpleasant taste of the drug is masked out, which is obtained by the method described above, preferably has a granular form such as powder, fine granule, granule, etc.

- 5       As the method of granulating such a drug-containing substance, any of *per se* known method can be used, and examples thereof include extrusion granulating method, crush granulating method, fluidized bed granulating method, centrifugal granulating method, rolling  
10 granulating method, high-speed stir granulating method, etc. In the flowing method, fluidized bed, centrifugal flow, air-permeable coating pan, high-speed stirring or a combination type equipment thereof can be used and a suitable equipment can be selected according to the  
15 shape, size and production method.

- The particle diameter of the drug-containing substance can be appropriately set according to the unpleasant taste (e.g. bitter taste, etc.) of the drug or the degree of masking. Since the drug-containing  
20 substance is finally taken in a state of being surrounded by a jelly, it is not necessary to pursue refining of particles for the purpose of improving the dispersion of the particles and avoiding foreignness, like the case of the dosage form of syrup. It is possible to use the  
25 drug-containing substance having a particle diameter of

up to about 2 mm and the particle diameter is not specifically limited, but is usually from 50 to 1800  $\mu\text{m}$ , preferably from 75 to 1500  $\mu\text{m}$ , and more preferably from 100 to 1000  $\mu\text{m}$ .

- 5           According to the desired particle diameter of the drug-containing substance, the masking method can be appropriately selected.

          In the case where the drug-containing substance in the form of fine particles having a particle diameter of  
10 up to 300  $\mu\text{m}$  (usually from 75 to 300  $\mu\text{m}$ , and preferably from 100 to 250  $\mu\text{m}$ ) is prepared, there can be preferably employed a method of preparing wax matrix type fine particles using a method of dispersing a drug in a fatty acid ester of glycerol base. If necessary, the resulting  
15 fine particles can also be film-coated by using a water-insoluble coating agent such as pH-dependent dissolution type polymer.

          The fatty acid ester of glycerol base includes, for example, glyceryl monostearate, citric acid and fatty  
20 acid esters of glycerol, glyceryl monobehenate, etc. The water-soluble coating agent such as pH-dependent dissolution type polymer includes, for example, aminoalkyl Methacrylate Copolymer E, Methacrylic acid Copolymer L, Methacrylic acid Copolymer LD,  
25 hydroxypropylmethylcellulose phthalate,



hydroxymethylcellulose acetate succinate, etc.

In this case, the mixing ratio of the drug to fatty acid ester of glycerol in the fine particles, and the amount of the coating agent vary depending on the kind of the drug, i.e. degree of the bitter taste of the drug and its release characteristics and, therefore, they are appropriately selected according to them. In the case of a drug having high water solubility and low threshold value of bitter taste (about several  $\mu\text{g/mL}$ ), the amount of the fatty acid ester of glycerol to be mixed with 1 part by weight of the drug contained in the fine particles is not less than 1.5 parts by weight, preferably not less than 2.5 parts by weight, and more preferably not less than 4 parts by weight. The upper limit of the amount of the fatty acid ester of glycerol in such a case is about 15 parts by weight.

The proportion of the coating film component based on 100% by weight of the core particles is usually from 10 to 100% by weight, preferably from 10 to 80% by weight, and more preferably from 10 to 60% by weight.

The above drug-containing substance can be prepared by the following method. First, the drug is molten or dispersed in a molten fatty acid ester of glycerol. Then, this melt is dropped on a disc rotating at high speed, using a proper liquid delivery pump. The dropped

melt is splashed by a centrifugal force of the disc and then solidified with cooling during the dropping to obtain microspherical particles. Then, a solution containing a coating film component is sprayed from a  
5 spray gun with allowing to flow the resulting microspherical particles in a fluidized bed granulator to form microspherical coated particles.

In the case where a comparative large drug-containing substance having a particle diameter of larger  
10 than 500  $\mu\text{m}$  is prepared, there can be preferably used a masking method of including a drug in gel beads such as water-insoluble alginate beads. In this case, the content of the drug can be usually set within a range from 10 to 90% by weight based on 100% by weight of the  
15 drug-containing substance, optionally. When the content is too small, penetration of water into beads is accelerated and release of the drug is promoted. Therefore, in the case of the drug which is freely soluble in water, the content is not less than 20% by  
20 weight, preferably from 20 to 90% by weight, and more preferably from 30 to 80% by weight.

The above drug-containing substance can be prepared, for example, by the following method. First, a drug is dispersed in an aqueous solution of sodium  
25 alginate. Then, the resulting suspension is added

dropwise in an aqueous solution containing a calcium salt such as calcium chloride. The added liquid droplets are immediately solidified by the reaction between alginic acid and calcium ions, thereby to form beads including the drug therein. The resulting beads are collected, washed and then dried to obtain masked particles (drug-containing substance).

Furthermore, the resulting masked particles may also be coated with the above proper coating agent, if necessary. In the case of coating with the water-soluble polymer such as gelatin, acacia, etc., it is possible to form a coating film by using the coacervation method before collecting the beads. That is, a polymer film made of gelatin is formed simultaneously with formation of alginic acid beads by previously mixing a polymer with an aqueous solution containing a calcium salt, adding dropwise an aqueous sodium alginate solution wherein a drug is suspended, and adding a coacervation inducer such as alcohol.

It is possible to mix various excipients, disintegrants, lubricants and other additives, which are usually used in the production of the drug, with the drug-containing substance, in addition to the drug and masking agent.

On the other hand, as the gelling agent used in the

pharmaceutical composition of the present invention, those requiring any treatment such as heating, cooling, etc. in the case of gelation are not suitable, but those having a property capable of gelling quickly at normal  
5 temperature when adding water are desirable. The gelling agent having such physical properties is preferably a polymer capable of causing crosslinking gelation in the presence of polyvalent metallic ions. The term "gelling agent" used in the present invention includes not only  
10 those composed of a single component, but also those capable of causing gelation by using two or more components in combination. The polymer capable of causing crosslinking gelation by an action of the polyvalent metallic ions includes, for example, alginate,  
15 pectic acid salt, etc. Among them, an alginate is preferred. The salt of the alginic acid and pectic acid includes, for example, salt of alkali metal such as sodium, potassium, etc.; salt of alkali earth metal such as calcium, etc.; or partially esterified one thereof.  
20 Among them, a sodium salt of alginic acid or pectic acid, particularly sodium alginate has great value in use because it is widely used as a viscous agent or a gelling agent in the field of foods and those having different molecular weights are commercially available.  
25       Regarding almost all of commercially available

sodium alginates, the viscosity in the form of an aqueous solution is defined. The viscosity of sodium alginate used in the present invention is from 20 to 1000 cP, preferably from 50 to 800 cP, and more preferably from 80 to 800 cP, in terms of the viscosity of an aqueous 1% solution at 20 °C (using a rotary viscometer at 30 rpm).

Regarding sodium alginate, a product having ultra-low viscosity defined as a viscosity of an aqueous 10% solution is commercially available. In the case of those having too low viscosity, it is difficult to obtain strong gel intensity. On the other hand, in the case of those having high viscosity, it becomes difficult to dissolve when adding water. In both cases, it becomes disadvantageous for masking of the drug.

In addition, sodium alginate is classified into various grades according to a composition ratio of mannuronic acid to guluronic acid as a constituent unit of the polymer, that is ratio M/G. Since the gelation of alginic acid due to metallic ions is based on chelete crosslinking in the guluronic acid moiety, the ratio M/G is large. That is, in the case of those containing a large amount of mannuronic acid, a soft gel is liable to be obtained and the ratio M/G is small. That is, in the case of those containing a small amount of mannuronic acid, a hard gel is liable to be obtained. The ratio M/G

of commercially available sodium alginate is from 0.3 to 2.5. In the present invention, a jelly having desired hardness can be prepared even when using any sodium alginate having the hardness within this range. It is possible to prepare a jelly having a desired strength by appropriately selecting the ratio M/G within a range from preferably 0.5 to 2, and more preferably from 1 to 2. The ratio M/G can be determined according to the method of Haug et al. (A. Haug et al., Carbohydrate Research 32, 10 (1974) 217-225).

Examples of the polyvalent metallic ion include ions of salt of alkali earth metal such as magnesium, calcium, etc.; and ions of salt of divalent /trivalent metal such as aluminum, iron, copper, zinc, etc. Among them, calcium ion is preferred as an additive of the medicine.

Examples of the supply component of the calcium ion include calcium salt of inorganic acid, such as calcium chloride, calcium sulfate, calcium monohydrogenphosphate, 20 calcium carbonate, etc.; and calcium salt of organic acid, such as calcium lactate, calcium gluconate, calcium citrate, etc. When using a salt, which is neutral and insoluble in water, such as calcium sulfate, calcium citrate, monohydrogenphosphate, calcium carbonate, etc. 25 among them, since ions are not emitted only by adding

water, it becomes necessary to add an acid for dissolving the salt. Therefore, in the present invention, it is also possible to add an organic acid such as citric acid, adipic acid, glucono- $\delta$ -lactone acid, etc.

- 5           It is very important for the gelling agent to form a homogeneous jelly as fast as possible when adding water. Since the gelation in the case of using sodium alginate and a calcium salt as the gelling agent occurs in the following two stages, that is (i) hydration of
- 10 sodium alginate and (ii) formation of a salt with calcium ions, partial gelation of alginic acid occurs in the case where sodium alginate has high viscosity and a long time is required for hydration or dissociation of the calcium salt occurs too fast, resulting in heterogeneous jelly.
- 15 Particularly, when using a salt, which is neutral and soluble in water, such as calcium chloride, calcium lactate, etc., calcium ions are emitted fast but partial gelation of alginic acid is intensively conducted. Therefore, the resultant is composed of two phases, i.e.
- 20 hard gel and a liquid portion and dissolution of the drug is sometimes accelerated. To overcome such a disadvantage, the gelation reaction can be delayed by adding sodium citrate or sodium pyrophosphate which has an chelate action to calcium ions.

- 25           The hardness of the jelly to be formed when water

is mixed with the pharmaceutical composition comprising a drug-containing substance wherein an unpleasant taste of the drug is masked out, and a gelling agent according to the present invention is not specifically limited. In  
5 view of the feel on taking and dispersed state of drug particles, the jelly preferably has a hardness enough to endure elasticity for shape retention. Such a hardness of the jelly can be controlled by appropriately selecting/controlling the kind and amount of the gelling  
10 agent, as a principal factor, as well as amount of water to be added on taking.

For example, when using sodium alginate and a calcium salt as the gelling agent, it is a mixing ratio of sodium alginate to water that decides the hardness of  
15 the jelly. The amount of sodium alginate to be mixed with water so as to obtain a jelly having a proper hardness varies depending on the specification viscosity and ratio M/G, but is from about 0.2 to 5% by weight, preferably from about 0.5 to 3% by weight, and more  
20 preferably from about 0.5 to 2% by weight. The hardness of the jelly includes, for example, hardness of the jelly thus prepared.

Since the pharmaceutical composition of the present invention is provided in a solid state and water is added  
25 by users, the dose is set by previously defining the



amount of water to be added on taking in the manufacturing of the preparation.

When the amount of the calcium salt to be mixed with the gelling agent is too small, the gelation becomes  
5 insufficient. On the other hand, even if the amount is too large, excess calcium salt causes a change in taste. The proper amount of the calcium salt is from 0.1 to 1.5 mol, preferably from 0.1 to 1 mol, and more preferably from 0.2 to 0.7 mol, per mol (molecular weight per  
10 carboxyl group: 198) of sodium alginate. In the case of a water-insoluble calcium salt, it is necessary to select an organic acid required for dissociation of it and to set the amount of the organic acid, carefully, because not only control of the gelation rate but also the taste  
15 of the jelly are influenced by them.

The gelling agent in the present invention preferably contains the sodium alginate and calcium salt describe above as a principal component, and may also contain organic acids, chelating agents, sweeteners (e.g.  
20 purified sucrose, saccharin sodium, thaumatin, aspartame, etc.) and flavors (e.g. cherry flavor, strawberry flavor, orange flavor, etc.).

In the pharmaceutical composition of the present invention, the mixing ratio of the drug-containing  
25 substance to the gelling agent is set by generally

evaluating in view of the feel on taking, bitter taste, etc., considering the volume of the jelly formed by adding water on taking, and the amount of the drug-containing substance dispersed therein. When the amount of the drug-containing substance (drug particles) is too large, since the resulting jelly has rough feel to the tongue and the particles are often made contacted with the tongue, there is a possibility of the appearance of the bitter taste, unfavorably, which is not preferred. To the contrary, when the amount of the gelling agent is too large, the requisite amount of water increases and it becomes difficult to take.

In the case of preparing by adding 2 to 20 mL of water to the pharmaceutical composition of the present invention in the dose per time on taking (e.g. 50 to 1000 mg of the drug-containing substance is contained), proper weight ratio of the drug-containing substance to the gelling agent is from 1:0.01 to 1:2, preferably from 1:0.025 to 1:1.2, and more preferably from 1:0.025 to 1:0.8, in terms of the amount of sodium alginate contained in the gelling agent.

As described above, the pharmaceutical composition of the present invention is basically composed of two components, i.e. a drug-containing substance wherein the bitter taste of the drug is masked out, and a gelling

agent, and these components may be separately packaged and mixed before use. In the manufacturing of the preparation, these components may be mixed after preparing separately. Alternatively, a preparation can  
5 be manufactured by mixing the drug-containing substance with the gelling agent component and granulating the mixture, or coating the drug-containing substance (in the granular form) with the gelling agent component. The pharmaceutical composition of the present invention  
10 includes any of these embodiments.

The present invention further includes the following embodiments.

- (1) A pharmaceutical composition comprising a drug-containing substance wherein an unpleasant taste of the  
15 drug is masked out, and a gelling agent.
- (2) The pharmaceutical composition according to (1), which is added to water before taking and is taken as a jelly-like preparation.
- (3) The pharmaceutical composition according to (1),  
20 wherein the drug-containing substance has a powdered or granular form.
- (4) The pharmaceutical composition according to (3), wherein the drug-containing substance has a form of fine particles obtained by dispersing the drug in a fatty acid  
25 ester of glycerol base and said fine particles may be

coated with a coating agent of one or more of a water-soluble polymer, a water-insoluble polymer, an acid-soluble polymer and an enteric polymer.

(5) The pharmaceutical composition according to (4),  
5 wherein the drug-containing substance contains a fatty acid ester of glycerol in an amount of 1.5 to 15 parts by weight based on 1 part of the drug.

(6) The pharmaceutical composition according to (4),  
wherein a proportion of the coating agent for coating the  
10 drug-containing substance is from 10 to 100% by weight based on 100% by weight of the non-coated drug-containing substance.

(7) The pharmaceutical composition according to (3),  
wherein the drug-containing substance in which the  
15 unpleasant taste of the drug is masked out is a substance in the form of fine particles obtained by including the drug in alginate beads.

(8) The pharmaceutical composition according to (7),  
which contains the drug in the proportion of 10 to 90% by  
20 weight based on 100% by weight of the drug-containing substance.

(9) The pharmaceutical composition according to (2),  
wherein the gelling agent is in a powdered or granular form.

25 (10) The pharmaceutical composition according to (3),

wherein the gelling agent is contained in the embodiment of coating the surface of the powdered or granular drug-containing substance.

(11) The pharmaceutical composition according to (1),  
5 wherein the gelling agent contains a polymer capable of gelling by a bridge action of polyvalent metallic ion as the gelling agent.

(12) The pharmaceutical composition according to (11),  
which contains sodium alginate and a calcium salt as the  
10 gelling agent.

(13) The pharmaceutical composition according to (12),  
wherein the gelling agent contains the calcium salt in a proportion of 0.1 to 1.5 mol based on 1 mol of sodium alginate.

15 (14) The pharmaceutical composition according to (12), wherein a mixing ratio by weight of the drug-containing substance to the gelling agent is from 1:0.01 to 1:2 in terms of a proportion of sodium alginate contained in the gelling agent.

20 (15) The pharmaceutical composition according to (1), wherein the drug is an antimicrobial drug or antibiotic having a bitter taste.

(16) The pharmaceutical composition according to (15), wherein the drug is a pyridonecarboxylic acid synthetic  
25 antimicrobial drug.

(17) The pharmaceutical composition according to (16), wherein the drug is a pyridonecarboxylic acid synthetic antimicrobial drug selected from the group consisting of enoxacin, norfloxacin, ofloxacin, levofloxacin,

5 cyprofloxacin, lomefloxacin, tosufloxacin, nadifloxacin, grepafloxacin, trovafloxacin and acid addition salts thereof.

(18) The pharmaceutical composition according to (2), wherein the drug is grepafloxacin or an acid addition  
10 salt thereof

(19) The pharmaceutical composition according to (4) or (7), wherein the gelling agent contains a polymer capable of gelling by a bridge action of polyvalentmetallic ion as the gelling agent.

15 (20) A method of producing a pharmaceutical composition wherein unpleasant taste of the drug is masked out, which comprises (1) preparing a drug-containing substance in which the unpleasant taste is masked out, (2) preparing a gelling agent capable of gelling at normal temperature  
20 when added to water, and (3) mixing the drug-containing substance and the gelling agent.

(21) A method of administering a drug having unpleasant taste to humans, which comprises mixing a drug-containing substance in which the unpleasant taste is masked out and  
25 a gelling agent capable of gelling at normal temperature

when added to water, adding the mixture to water under stirring and taking the resulting composition orally.

#### Examples

The following Examples further illustrate the pharmaceutical composition of the present invention in detail, but the present invention is not limited by these Examples.

#### Example 1

##### (A) Drug-containing substance

After 90g of fatty acid ester of glycerol was molten at about 100 °C, 10 g of grepafloxacin hydrochloride was added and dispersed therein by using a homogenizer after sufficiently compatibilizing. The resultant was granulated with cooling on a rotary table under the conditions of a revolving speed of 2000 rpm to obtain 100 g of homogeneous microspherical particles (average particle diameter: about 150 μm).

##### (B) Gelling agent

8 g of sodium alginate, 1.6 g of sodium citrate, 0.8 g of calcium lactate, 8 g of adipic acid and 183.6 g of powdered sucrose were mixed to obtain 202 g of a gelling agent powder.

100 g of the drug-containing particles and 202 g of the powder of the gelling agent, thus obtained, were mixed to obtain a powdered composition of the present

invention. To 1.5 g of the composition was added 5 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

## 5 Example 2

### (A) Drug-containing substance

After 84 g of fatty acid ester of glycerol was molten at about 100 °C, 15 g of grepafloxacin hydrochloride and 1 g of calcium monohydrogen phosphate  
10 were added and dispersed therein by using a homogenizer after sufficiently compatibilizing. The resultant was granulated with cooling on a rotary table under the conditions of a revolving speed of 2000 rpm to obtain 100 g of homogeneous microspherical particles (average  
15 particle diameter: about 150  $\mu\text{m}$ ).

### (B) Gelling agent

8 g of sodium alginate, 1.6 g of sodium citrate, 0.8 g of calcium monohydrogen phosphate, 8 g of adipic acid and 183.6 g of powdered sucrose were mixed to obtain  
20 202 g of a gelling agent powder.

100 g of the drug-containing particles and 202 g of the powder of the gelling agent, thus obtained, were mixed to obtain a powdered composition of the present invention. To 1.5 g of the composition was added 5 ml Of  
25 water with a few minutes of stirring to obtain a jelly-



like composition wherein the drug-containing particles are dispersed.

### Example 3

#### (A) Drug-containing substance

5           After 9 kg of fatty acid ester of glycerol was molten at about 100 °C, 1 kg of grepafloxacin hydrochloride was dispersed therein and the resultant was granulated with spray cooling by using a spray drying equipment under the conditions of an inlet-air  
10 temperature of 50 °C and an atomizer revolving speed of 10000 rpm. As a result, 10 kg of a 10% grepafloxacin hydrochloride pharmaceutical composition (average particle diameter: about 150 µm) was obtained.

#### (B) Gelling agent

15           800 g of sodium alginate, 80 g of calcium gluconate, 80 g of citric acid and 18.3 kg of powdered sucrose were mixed and then granulated by rotary fluidized bed granulator (New Marumerizer, manufactured by Fuji Paudal Co.,Ltd.) to obtain 19.26 kg of a  
20 granulated powder (average particle diameter: about 20 µm) of a gelling agent.

10 kg of the drug-containing particles and 19.26 kg of the granulated powder of the gelling agent, thus obtained, were mixed to obtain 29.26 kg of a granulated  
25 powdered composition for jelly preparation of the present

invention. To 1.5 g of the granulated powdered composition was added 5 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

5 Example 4

(A) Drug-containing substance

After 500 g of the microspherical particles obtained in Example 3 were charged in a rotary fluidized bed granulation coating equipment (NQ-125, manufactured  
10 by Fuji Paudal Co., Ltd.) and the inlet-air temperature and product temperature were controlled to 60 °C and 30-40 °C, respectively, 1500 g of 25 % Methacrylic acid Copolymer LD suspension [containing 1000 g of Eudragit L30D55, (manufactured by Rohm Pharma Co., Ltd.), 30 g of  
15 triethyl citrate and 290 g of purified water] was sprayed on the microspherical particles, and then dried to obtain a coated powder (average particle diameter: about 200 to 250 µm).

(B) Gelling agent

20 400 g of sodium alginate, 40 g of calcium monohydrogenphosphate, 80 g of sodium citrate, 260 g of adipic acid, 20 g of a flavor, 2 g of a colorant Food Red No. 2, 100 g of aspartame and 9000 g of powdered sucrose were mixed to obtain a gelling agent powder.

25 850 g of the drug-containing particles and 9000 g

of the gelling agent powder, thus obtained, were mixed to obtain a powdered composition for jelly preparation of the present invention. To 5 g of the powdered composition was added 10 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

#### Example 5

##### (A) Drug-containing substance

After 500 g of the microspherical particles obtained in Example 3 were charged in a rotary fluidized bed granulation coating equipment (NQ-125, manufactured by Fuji Paudal Co., Ltd.) and the inlet-air temperature and product temperature were controlled to 60 °C and 35-40 °C, respectively, ethylcellulose (Aquacoat made of FMC: manufactured by Asahi Chemical Industry Co., Ltd.) was sprayed on the microspherical particles in the proportion of 25 to 100% to obtain a coated powder (average particle diameter: about 200 to 250  $\mu$ m).

##### (B) Gelling agent

400 g of sodium alginate, 20 g of calcium carbonate, 200 g of adipic acid, 20 g of a flavor, 2 g of a colorant Food Red No. 2 and 11650 g of purified sucrose were mixed to obtain a gelling agent powder.

500 g of the drug-containing particles and 10000 g of the gelling agent powder, thus obtained, were mixed to

obtain a powdered composition for jelly preparation of the present invention. To 4 g of the powdered composition was added 10 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

#### Example 6

##### (A) Drug-containing substance

After 500 g of the microspherical particles obtained in Example 3 were charged in a rotary fluidized bed granulation coating equipment (NQ-125, manufactured by Fuji Paudal Co., Ltd.) and the inlet-air temperature and product temperature were controlled to 60 °C and 35-40 °C, respectively, a mixed film of ethylcellulose (Aguacoat made of FMC: manufactured by Asahi Chemical Industry Co., Ltd.) and hydroxypropylmethylcellulose (TC-5E, manufactured by Shin-Etsu Chemical Co., Ltd.) was sprayed on the microspherical particles in the proportion of 25 to 100% to obtain a coated powder (average particle diameter: about 200 to 250 μm).

##### 20 (B) Gelling agent

400 g of sodium alginate, 40 g of calcium monohydrogenphosphate, 200 g of adipic acid, 20 g of a flavor, 2 g of a colorant Food Red No. 2 and 11650 g of purified sucrose were mixed to obtain a gelling agent powder.

500 g of the drug-containing particles and 10000 g of the gelling agent powder, thus obtained, were mixed to obtain a powdered composition for jelly preparation of the present invention. To 5 g of the powdered composition was added 10 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

#### Example 7

##### (A) Drug-containing substance

10 After 500 g of the microspherical particles obtained in Example 3 were charged in a rotary fluidized bed granulation coating equipment (NQ-125, manufactured by Fuji Paudal Co., Ltd.) and the inlet-air temperature and product temperature were controlled to 60 °C and 35-40  
15 °C, respectively, a mixed film of Aquacoat made of FMC (manufactured by Asahi Chemical Industry Co., Ltd.) and mannitol (manufactured by Kyowa Hakko Kogyo Co., Ltd.) was sprayed on the microspherical particles in the proportion of 25 to 100% to obtain a coated powder  
20 (average particle diameter: about 200 to 250  $\mu$ m).

##### (B) Gelling agent

400 g of sodium alginate, 40 g of calcium monohydrogenphosphate, 200 g of adipic acid, 20 g of a flavor, 2 g of a colorant Food Red No. 2 and 11650 g of  
25 powdered sucrose were mixed to obtain a gelling agent

powder.

500 g of the drug-containing particles and 10000 g of the gelling agent powder, thus obtained, were mixed to obtain a powdered composition for jelly preparation of the present invention. To 5 g of the powdered composition was added 10 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

#### Example 8

10 In addition to 100 g of the microspherical particles (drug-containing substance) obtained in Example 3, 8 g of sodium alginate, 0.8 g of calcium sulfate, 8 g of citric acid, 0.2 g of a strawberry flavor, 0.02 g of a colorant Food Red No. 2 and 183 g of powdered sucrose  
15 were charged in a rotary fluidized bed granulator (MP-01, manufactured by Powrex Co., Ltd.) and the inlet-air temperature and product temperature were controlled to 60 °C and 35-40 °C, respectively, the mixture was granulated and dried using a 5% solution of hydroxypropyl cellulose  
20 (HPC-L) as a binder to obtain a powdered composition for jelly (average particle diameter: about 250  $\mu$ m) according to the present invention. To 1 g of the powdered composition was added 2 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the  
25 drug-containing particles are dispersed.

## Example 9

In addition to 100 g of the microspherical particles (drug-containing substance) obtained in Example 3, 8 g of sodium alginate, 0.8 g of calcium citrate, 8 g of citric acid, 0.2 g of a strawberry flavor, 0.02 g of a colorant Food Red No. 2 and 183 g of powdered sucrose were charged in a flow granulating equipment (MP-01) and the inlet-air temperature and product temperature were controlled to 60 °C and 35-40 °C, respectively, the mixture was granulated and dried using a 5% solution of hydroxypropylmethylcellulose (HPMC) as a binder to obtain a powdered composition for preparation of jelly (average particle diameter: about 250  $\mu$ m) according to the present invention. To 1 g of the powdered composition was added 2 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

## Example 10

After 500 g of the microspherical particles (drug-containing substance) obtained in Example 3 were charged in a centrifugal coating granulator (CF-360, manufactured by Freund Industry Co., Ltd.), the particles were granulated with scattering a mixed powder containing 40 g of sodium alginate, 4 g of calcium citrate, 40 g of citric acid, 1 g of a strawberry flavor, 0.1 g of a

colorant Food Red No. 2 and 915 g of powdered sucrose using 150 g of purified water, and then dried to obtain a granulated composition for preparation of jelly according to the present invention. To 2 g of the granulated  
5 composition was added 4 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

#### Example 11

In addition to 255 g of the microspherical  
10 particles (drug-containing substance) obtained in Example 4, a gelling agent component containing 12 g of sodium alginate, 1.2 g of calcium monohydrogen phosphate, 7.5 g of citric acid, 2.4 g of sodium citrate, 0.6 g of a strawberry flavor, 0.06 g of a colorant Food Red No. 2, 3  
15 g of a thaumatin, 2.25 g of a  $\beta$ -cyclodextrine and 270 g of powdered sucrose were charged in a rotary fluidized bed granulator (MP-01, manufactured by Powrex Co., Ltd.) and the inlet-air temperature and product temperature were controlled to 60 °C and 35-40 °C, respectively, the  
20 mixture was granulated by using a 5% solution of hydroxypropyl cellulose (HPC-L) as a binder, and dried to obtain a powdered composition for preparation of jelly (average particle diameter: about 250  $\mu$ m) according to the present invention.

25 To, 2 g of the powdered composition was added, 4 ml



of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

#### Example 12

##### 5 (A) Drug-containing substance

To 300 mL of an aqueous 2 w/v% solution of sodium alginate, 10 g of grepafloxacin hydrochloride and an equimolar amount of sodium hydroxide were added and suspended. The resulting suspension was added dropwise  
10 in 3L of an aqueous calcium chloride solution (1 w/v%) via a nozzle having an inner diameter of 0.5 mm to form gel beads. The resulting beads were allowed to stand in an aqueous calcium chloride solution for 2 hours, collected and then washed with water and acetone. The  
15 beads were air-dried for 12 hours and then vacuum-dried at room temperature for 2 hours to obtain 10 g of drug particles wherein the content of the drug is 60 w/w% and the diameter is 0.8 mm.

##### (B) Gelling agent

20 4 g of sodium alginate, 0.4 g of calcium monohydrogenphosphate, 0.8 g of sodium citrate, 2.6 g of adipic acid, 0.2 g of a strawberry flavor, 0.02 g of a colorant Food Red No. 2, 1 g of aspartame and 90 g of purified sucrose were mixed to obtain a gelling agent  
25 powder.

10 g of the drug-containing particles and 90 g of the gelling agent powder, thus obtained, were mixed to obtain a composition for jelly preparation of the present invention.

- 5           To 1 g of the powdered composition was added 3 mL of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

Example 13

- 10           After 395 g of the drug-containing particle obtained by a similar method to Example 12 were charged in a centrifugal coating granulator (CF-360, manufactured by Freund Industry Co., Ltd.), 1690 g of an aminoalkyl Methacrylate Copolymer E solution (7%) containing 140 g  
15 of aminoalkyl Methacrylate Copolymer E (Eudragit E100) and 60 g of talc in a mixture solution of ethanol (1400g) and purified water (400g) was sprayed on the above particles to obtain a coated particle (drug-containing substance).
- 20           After 200 g of the coated granules were charged in a centrifugal coating granulator (CF-360, Freund Industry Co., Ltd.), the particles were granulated with scattering a gelling agent component containing 80 g of sodium alginate, 8 g of calcium monohydrogen phosphate, 16 g of  
25 citric acid, 50 g of adipic acid, 4 g of strawberry

flavor, 0.4 g of a colorant Food Red No. 2 and 1840 g of powdered sucrose to obtain a gelling agent composition (granule diameter; 1000 to 2500  $\mu\text{m}$ ) of the present invention.

- 5           To 1.3 g of the composition was added 4 mL of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

Example 14

- 10           After 400 g of the drug-containing particles obtained by a similar method to Example 12 were charged in a flow granulating equipment (NQ-125, manufactured by Fuji Paudal Co., Ltd.), and the inlet-air temperature and product temperature were controlled to 60 °C and 30 to 40  
15 °C, respectively, 80 g of a methacrylic acid copolymer LD solution (25 %) [a mixed suspension containing 1000 g of Eudragit L30D55 (manufactured by Rohm Pharma Co., Ltd.), 30 g of triethyl citrate and 290 g of purified water] was sprayed on the particles to obtain a coated particle  
20 (drug-containing substance).

          After 200 g of the coated granules were charged in a centrifugal coating granulator (CF-360 manufactured by Freund Industry Co. Ltd.), the particules were granulated with scattering a gelling component containing 80 g of  
25 sodium alginate, 8 g of calcium monohydrogen phosphate,

16 g of sodium citrate, 50 g of adipic acid, 4 g of a  
strawberry flavor, 0.4 g of a colorant Food Red No. 2 and  
1840 g of powdered sucrose to obtain a gelling agent  
composition (granule diameter; 850 to 2000  $\mu\text{m}$ ) of the  
5 present invention.

To 1 g of the composition was added 3 mL of water  
with a few minutes of stirring to obtain a jelly-like  
composition wherein the drug-containing particles are  
dispersed.

10 Example 15

(A) Drug-containing substance

After 400 g of purified sucrose was charged in a  
centrifugal coating granulator (CF-360, manufactured by  
Freund Industry Co. Ltd.), a granulate was obtained by  
15 using 130 g of purified water with scattering a mixture  
of 120 g of grepafloxacin hydrochloride, 200 g of  
purified sucrose and 280 g of corn starch. Subsequently,  
the resulting granule was coated with  
hydroxypropylmethylcellulose phthalate and an  
20 ethylcellulose solution (containing 150 g of  
hydroxypropylmethylcellulose phthalate (HPMCP HP-55S,  
manufactured by Shin-Etsu Chemical Co., Ltd.), 120 g of  
ethylcellulose "ETHOCEL STD 10CPS" (manufactured by Dow  
Chemical Co.) and 1.5 g of fatty acid ester of glycerol  
25 ("Myvacet 9-40T", manufactured by Koyo Shokai Co.) as a

plasticizer in 2500 g of ethanol and 2500 g of dichloromethane) using the spray system, dried at 60 °C and adjusted to obtain spherical masked particles having a particle diameter of 0.25 to 1 mm.

5 (B) Gelling agent

120 g of sodium alginate, 20 g of calcium lactate, 24 g of sodium citrate, 6 g of a flavor, 0.6 g of a colorant Food Red No. 2 and 1128 g of purified sucrose were mixed to obtain a gelling agent powdered  
10 composition.

1000 g of the drug-containing particles and 1000 g of the gelling agent powder, thus obtained, were mixed to obtain a composition for jelly preparation of the present invention. To 0.5 g of the composition was added 3 ml of  
15 water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

Example 16

(A) Drug-containing substance

20 After 1080 g of purified sucrose was charged in a centrifugal coating granulator (CF-360, manufactured by Freund Industry Co., Ltd.), a granulate was obtained by using 250 g of purified water with scattering a mixture of 1350 g of grepafloxacin hydrochloride and 400 g of  
25 lactose. The resulting granule was dried at 50 °C and

sieved to obtain spherical particles having a particle diameter of 0.25 to 2 mm. Subsequently, 2800 g of the resulting particles were coated with hydroxypropylmethylcellulose and an ethylcellulose solution (containing 52 g of hydroxypropylmethylcellulose (HPMC TC-5R, manufactured by Shin-Etsu Chemical Co., Ltd.), 139 g of ethylcellulose "ETHOCEL STD 10CPS" (manufactured by Dow Chemical Co.), 19 g of fatty acid ester of glycerol ("Myvacet 9-40T", manufactured by Koyo Shokai Co.) as a plasticizer in 3093 g of ethanol and 515 g of purified water) using the spray system, dried at 40 °C and sieved to obtain spherical masked particles having a particle diameter of 0.25 to 2 mm.

(B) Gelling agent

360 g of sodium alginate, 35 g of calcium sulphate, 150 g of gluconodeltalactone, 18 g of a flavor, 1.8 g of a colorant Food Red No. 2 and 3400 g of purified sucrose were charged in a spiler flow (model FLO-5 manufactured by Fleund Industry Co., Ltd.) and granulated using 2000 g of a 5% HPC-L solution (average particle diameter: 75 to 1000  $\mu$ m).

3000 g of the drug-containing particles and 4000 g of the gelling agent powder, thus obtained, were mixed to obtain a powdered composition for jelly preparation of the present invention. To 0.6 g of the powdered

composition was added 5 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

#### Example 17

##### 5 (A) Drug-containing substance

After 500 g of purified sucrose were charged in a centrifugal flow type coating granulator (CF-360 manufactured by Freund Industry Co. Ltd.), a granulate was obtained by scattering a mixture of 297 g of  
10 grepafloxacin hydrochloride and 300 g of powdered sucrose with a 145 g of 3 % solution of hydroxypropylcellulose (HPC-L) as a binder. The resulting granule was dried at 50 °C for 12 hours to obtain a granular particle having a particle diameter of 355 to 850  $\mu\text{m}$ . Subsequently, after  
15 500 g of the resulting particles were charged in a centrifugal flow type coating granular (CF-360 manufactured by Freund Industry Co. Ltd.), a granulate was obtained by using 110 g of hydroxypropylcellulose (3 %) with scattering 500 g of powdered sucrose and dried at  
20 50 °C for 12 hours to obtain a granular particle having diameter of 500 to 1000  $\mu\text{m}$ .

900 g of the resulting granular particles were charged in a centrifugal flow type coating granular, and a hydroxypropylmethylcellulose solution (5%) containing  
25 50 g of hydroxypropylmethylcellulose (TC-5R, manufactured

by Shin-Etsu Chemical Co., Ltd. ) in 475 g of ethanol and 475 g of purified water was sprayed on the particles, and dried at 60 °C and sieved to obtain a spherical particle having a particle diameter of 500 to 1000 µm.

- 5        Subsequently, 400 g of the resulting spherical particle were charged in a rotary fluidized bed granulator (NQ-125, manufactured by Fuji Paudal Co., Ltd.), a methacrylic acid copolymer LD solution [containing 30 g of triethyl citrate, 1000 g of
- 10 methacrylic acid copolymer LD (Eudragit L30D55, manufactured by Rohm Pharma Co., Ltd.)] and 290 g of purified water was sprayed on the particles in the proportion of 10 to 50 % to obtain a coated particle. Further, an aminoalkyl Methacrylate Copolymer E solution
- 15 containing 20 g of talc and 80 g of aminoalkyl Methacrylate Copolymer E (Eudragit E 100, manufactured by Rhom Pharma Co., Ltd.) in 810 g of ethanol and 90 g of purified water was coated on the resulted particles in the proportion of 5 to 50 % to obtain a double coated
- 20 particle. The resulted particles were dried at 40 °C and sieved to obtain drug-containing particles having a particle diameter of 500 to 2000 µm.

(B) Gelling agent

- 400 g of purified sucrose were charged in a
- 25 centrifugal coating granular (CF-360, manufactured by



Freund Industry Co., Ltd.) and granulated with scattering a powder mixture of 40 g sodium alginate, 4 g of calcium monohydrogenphosphate, 8 g of sodium citrate, 25 g of adipic acid, 2 g of a strawberry flavor, 0.2 g of a colorant Food Red No.2 and 520 g of powdered sucrose by using purified water as a binder to obtain a gelling agent particle having a particle diameter of 1000 to 2000  $\mu\text{m}$ . 200 g of the drug-containing particles and 400 g of the gelling agent particles, thus obtained, were mixed to obtain a jelly preparation of the present invention.

To 1.5 g of the resulted composition were added 3 ml of water with a few minutes of stirring to obtain a jelly-like composition wherein the drug-containing particles are dispersed.

Example 18

500 g of the drug-containing particles obtained by a similar method to Example 17 were charged in a centrifugal coating granular (CF-360, manufactured by Freund Industry Co., Ltd.) and granulated with scattering a gelling agent component containing 80 g of sodium alginate, 8 g of calcium monohydrogenphosphate, 16 g of sodium citrate, 50 g of citric acid, 4 g of a strawberry flavor, 0.4 g of a colorant Food Red No.3 and 1840 g of powdered sucrose by using purified water as a binder to obtain a gelling agent composition having a particle

diameter 1000 to 2500  $\mu\text{m}$  according to the present invention.

To 1.5 g of the resulted composition were added 3 ml of water with a few minutes of stirring to obtain a  
5 jelly-like composition wherein the drug-containing particles are dispersed.

#### Examples 19 to 21

In the same manner as in Examples 1, except for using ofloxacin, cyprofloxacin hydrochloride and  
10 lomefloxacin hydrochloride in place of grepafloxacin hydrochloride, the pharmaceutical compositions of the present invention can be prepared.

#### Experiment Example 1

With respect to the powdered compositions for jelly  
15 prepared in Example 4 and Example 12, the bitter taste was evaluated by an organoleptic test due to eleven subjects.

Specifically, in the case of the powdered composition for jelly of Example 4, a jelly-like sample  
20 was prepared by mixing 5 g of the powdered composition with 10 ml of water (at normal temperature of 15 to 25  $^{\circ}\text{C}$ ), followed by stirring. In the case of the powdered composition for jelly of Example 12, a jelly-like sample was prepared by mixing 1 g of the powdered composition  
25 with 3 ml of water (at normal temperature of 15 to 25

°C), followed by stirring. The resulting jelly-like samples were orally administered to the respective subjects. A syrup, which is prepared by suspending each of drug-containing substances obtained in the respective

5 Examples in a 30% sucrose solution containing 0.7% carboxymethylcellulose sodium (CMC·Na), not in the gelling agent, was orally administered to the respective subjects in the same manner as described above, as a control test. The results are shown in Table 1.

Table 1

	Example 4		Example 12	
	Jelly of the present invention	Syrup as control	Jelly of the present invention	Syrup as control
Number of persons who did not feel a bitter taste	7	1	8	2
Number of persons who felt a weak bitter taste	3	5	3	2
Number of persons who felt an ordinary bitter taste	1	3	0	4
Number of persons who felt a strong bitter taste	0	2	0	2
Number of persons who felt a very strong bitter taste	0	0	0	1

As is shown in Table 1, it became apparent that the pharmaceutical composition (formed into a jelly preparation before use) of the present invention effectively inhibit a bitter taste which appears when  
5 forming into a syrup.

#### Experimental Example 2

Jelly compositions prepared in Example 11 and Example 14 were subjected to a dissolution out test according to a dissolution test method, the second method  
10 (paddle method) of the Japanese Pharmacopoeia.

Specifically, 2 g (50 mg as the drug) of the composition for jelly of Example 11 was jelled by adding 4 mL of water. The jelled product was added to 500 mL of the second solution for the disintegration test according  
15 to the Japanese Pharmacopoeia, and the drug solution rate was measured every predetermined time under the condition of a temperature of 37 °C, the paddle rotation of 100rpm. Similarly, 1 g (50 mg as the drug) of the composition for  
jell of Example 14 was jelled by adding 3 mL of water and  
20 subjected to the same test.

The respective control samples, which contain the drug-containing substance only (50 mg as the drug) without containing the gelling agent in the respective compositions of Example 11 and 14, were subjected to the  
25 same dissolution test. Namely, the control sample for

the composition of Example 11 corresponds to the drug-containing substance obtained in Example 4, and the control sample for the composition of Example 14 corresponds to the coated product obtained by coating  
5 methacrylic acid copolymer LD on the drug-containing substance prepared in Example 12.

The results are shown in Figs. 1 and 2.

From the results, it was proved that the solution rate of the drug-containing substance only is not almost affected  
10 by the jelly composition. The results show that the pharmaceutical composition of the present invention is useful for masking the drug flavor under the condition that the absorption of the drug is not almost affected.

Industrial Applicability

15 The present invention makes it possible to conduct masking of a drug having unpleasant taste by taking, as a form on taking, the form of jelly wherein the drug whose unpleasant taste is masked out are dispersed and included. Even if masking of the drug-containing  
20 substance is insufficient for securing the bioavailability thereby to cause leakage of the drug in the mouth on taking, diffusion of the drug is inhibited because a medium is in the form of jelly and,  
furthermore, the drug-containing substance is taken in a  
25 state of being surrounded by a jelly and is hardly

remained in the mouth.

The composition of the present invention is used in combination with water in a proper amount when administered, unlike a coated drug such as conventional  
5 sugar-coated tablet, film-coated tablet, etc., it is possible to control the dose and is optimum for application to a child drug. Furthermore, the form of a jelly is easily taken and is also useful as an oral dosage form to infants, patients suffering from  
10 dysphagia, and aged persons.

The disclosure of Japanese Patent Application Serial No.10-217517, filed on July 31, 1998, is incorporated herein by reference.

## CLAIMS

1. A pharmaceutical composition comprising a drug-containing substance wherein an unpleasant taste of the drug is masked out, and a gelling agent.
- 5 2. The pharmaceutical composition according to claim 1, which is added to water before taking and is taken as a jelly-like preparation.
3. The pharmaceutical composition according to claim 1, wherein the drug-containing substance has a powdered or  
10 granular form.
4. The pharmaceutical composition according to claim 3, wherein the drug-containing substance has a form of fine particles obtained by dispersing the drug in a fatty acid ester of glycerol base and said fine particles may be  
15 coated with a coating agent of one or more of a water-soluble polymer, a water-insoluble polymer, an acid-soluble polymer and an entric polymer.
5. The pharmaceutical composition according to claim 4, wherein the drug-containing substance contains a fatty  
20 acid ester of glycerol in an amount of 1.5 to 15 parts by weight based on 1 part of the drug.
6. The pharmaceutical composition according to claim 4, wherein a proportion of the coating agent for coating the drug-containing substance is from 10 to 100% by weight  
25 based on 100% by weight of the non-coated drug-containing



substance.

7. The pharmaceutical composition according to claim 3, wherein the drug-containing substance in which the unpleasant taste of the drug is masked out is a substance in the form of fine particles obtained by including the drug in alginate beads.

8. The pharmaceutical composition according to claim 7, which contains the drug in the proportion of 10 to 90% by weight based on 100% by weight of the drug-containing substance.

9. The pharmaceutical composition according to claim 2, wherein the gelling agent is in a powdered or granular form.

10. The pharmaceutical composition according to claim 3, wherein the gelling agent is contained in the embodiment of coating the surface of the powdered or granular drug-containing substance.

11. The pharmaceutical composition according to claim 1, wherein the gelling agent contains a polymer capable of gelling by a bridge action of polyvalent\_metallic ion as the gelling agent.

12. The pharmaceutical composition according to claim 11, which contains sodium alginate and a calcium salt as the gelling agent.

13. The pharmaceutical composition according to claim

12, wherein the gelling agent contains the calcium salt in a proportion of 0.1 to 1.5 mol based on 1 mol of sodium alginate.

14. The pharmaceutical composition according to claim

5 12, wherein a mixing ratio by weight of the drug-containing substance to the gelling agent is from 1:0.01 to 1:2 in terms of a proportion of sodium alginate contained in the gelling agent.

15. The pharmaceutical composition according to claim 1,

10 wherein the drug is an antimicrobial drug or antibiotic having a bitter taste.

16. The pharmaceutical composition according to claim

15, wherein the drug is a pyridonecarboxylic acid synthetic antimicrobial drug.

15 17. The pharmaceutical composition according to claim

16, wherein the drug is a pyridonecarboxylic acid synthetic antimicrobial drug selected from the group consisting of enoxacin, norfloxacin, ofloxacin, levofloxacin, ciprofloxacin, lomefloxacin, tosufloxacin, nadifloxacin, grepafloxacin, trovafloxacin and acid addition salts thereof.

18. The pharmaceutical composition according to claim 2, wherein the drug is grepafloxacin or an acid addition salt thereof

25 19. The pharmaceutical composition according to claim 4

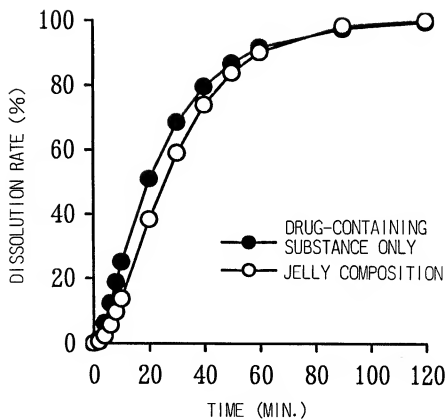
or 7, wherein the gelling agent contains a polymer capable of gelling by a bridging action of polyvalent metallic ion as the gelling agent.

20. A method of producing a pharmaceutical composition  
5 wherein unpleasant taste of the drug is masked out, which comprises (1) preparing a drug-containing substance in which the unpleasant taste is masked out, (2) preparing a gelling agent capable of gelling at normal temperature when added to water, and (3) mixing the drug-containing  
10 substance and the gelling agent.

21. A method of administering a drug having unpleasant taste to humans, which comprises mixing a drug-containing substance in which the unpleasant taste is masked out and a gelling agent capable of gelling at normal temperature  
15 when added to water, adding the mixture to water under stirring and taking the resulting composition orally.

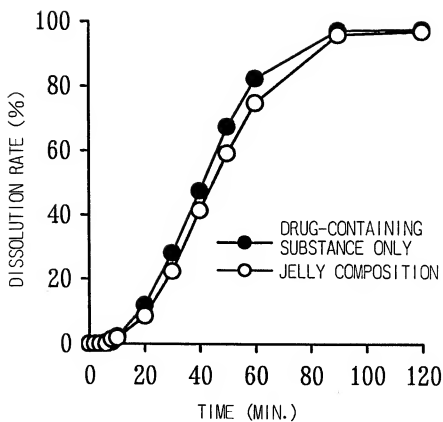
1/2

FIG.1



2/2

FIG.2



# INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/JP 99/04046

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K9/16 A61K9/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 826 376 A (TAISHO PHARMA CO LTD) 4 March 1998 (1998-03-04) page 4 -page 5; examples 2,9 ---	1-6,9, 15,20,21
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X	EP 0 855 183 A (HOECHST AG) 29 July 1998 (1998-07-29)  page 3, line 20 - line 38 page 3 -page 5; examples 1-3 ---	1-3,9, 15-17, 20,21

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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/> Patent family members are listed in annex
<p>Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>	
Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2000	20/01/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Boulois, D

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 99/04046

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 88 06893 A (BENZON PHARMA AS) 22 September 1988 (1988-09-22)  page 21 -page 24; examples 2-4 page 1, line 6 - line 11 page 4, line 35 - line 36 -----	1-3, 9-11, 20, 21
A	EP 0 841 062 A (DAIICHI SEIYAKU CO) 13 May 1998 (1998-05-13) page 5; example 3 -----	1-21

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/04046

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3 (partially), 4-6, 9-21 (partially)

Taste masking composition comprising drug containing substances obtained by dispersing the drug in a fatty ester of glycerol, possibly coated

2. Claims: 1-3 (partially), 7, 8, 9-21 (partially)

Taste masking composition comprising drug containing substances obtained by including the drug in alginate beads

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 99/04046

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